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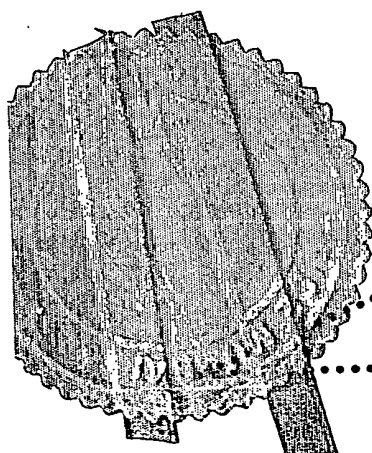
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Mumbai - 400 013

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy  
of Application and Provisional Specification filed on 3/11/2003 in respect of Patent Application  
No. 1154/MUM/2003 of CADILA HEALTHCARE LIMITED, a company incorporated under  
the Companies Act, 1956 of Zydus Tower, Satellite Cross Roads, Ahmedabad - 380 015,  
Gujarat, India.

This certificate is issued under the powers vested in me under  
Section 147(1) of the Patents Act, 1970.

.....



..... Dated this 23<sup>rd</sup> day of February 2004.

  
(R. BHATTACHARYA)

ASST. CONTROLLER OF PATENTS & DESIGNS.

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FORM 1

THE PATENTS ACT, 1970

APPLICATION FOR GRANT OF PATENT  
(See Sections 5(2), 7, 54 and 135 and Rule 33A)

(1) We, CADILA HEALTHCARE LIMITED, a company incorporated under the Companies Act, 1956, of Zydus Tower, Satellite Cross Roads, Ahmedabad 380 015, Gujarat, India

(2) hereby declare -

(a) That we are in possession of an invention titled

'Improved Process for the preparation of different forms of (S)-(+)-Clopidogrel bisulfate'

(b) That the Provisional Specification relating to this invention is filed with this application;

(c) That there is no lawful ground of objection to the grant of a patent to us.

(3) Further declare that the true and first inventor for the said invention are .

- (a) LOHRAV, Braj Bhushan,
- (b) LOHRAV, Vidya Bhushan,
- (c) PANDEY, Bipin,
- (d) DAVE, Mayank Ghanshyambhai

all Indian citizens, of CADILA HEALTHCARE LIMITED, Zydus towers, Satellite Cross Roads, Ahmedabad - 380 015, Gujarat, India

(4) We claim priority from the application(s) filed in the following convention country(ies), particulars of which are as follows: NIL

(5) That we are the assignees of the true and first inventors,

(6) That our address for service in India is as follows;

M/s Subramaniam, Natraj & Associates  
Attorneys-At-Law  
E-556, Greater Kailash-II  
New Delhi - 110 048, India.

Phone: +91 11 29215603, 29226012, 29216025  
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1154/MUM/2003  
3/11/2003

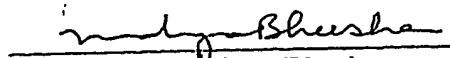
Received No. 2003/11/03  
Date of M.O.P.O. 23/11/03  
VDO Entry No. 5410  
Registrar of Valuation, Mumbai


(7) Following declaration was given by the inventors

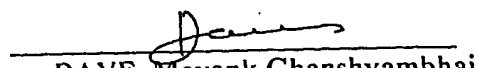
We, LOHRAY, Braj Bhushan; LOHRAY, Vidya Bhushan; PANDEY, Bipin and DAVE, Mayank Ghanshyambhai, all Indian citizens, of CADILA HEALTHCARE LIMITED, Zydus Towers, Satellite Cross Roads, Ahmedabad - 380 015, Gujarat, India,

and the true and first inventors for this invention declare that the applicants herein is our assignees.

  
LOHRAY, Braj Bhushan

  
LOHRAY, Vidya Bhushan

  
PANDEY, Bipin

  
DAVE, Mayank Ghanshyambhai

(8) That to the best of our knowledge, information and belief the facts and matters stated herein are correct and there is no lawful ground of objection to the grant of patent to us on this application.

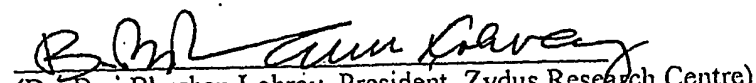
(9) Following are the attachments with this application:

- (a) Provisional specification in triplicate
- (b) Statement and Undertaking on FORM 3 in duplicate
- (c) Power of Authority
- (d) Form 2 in triplicate
- (e) Power of Authority
- (f) Abstract

Fee Rs. .... in Cash/Cheque/Bank Draft Bearing No..... dated.....on  
.....Bank.

We request that a patent be granted to us on any complete specification filed on this application for the said invention.

Dated this 1st day of NOVEMBER, 2003.

  
(Dr. Braj Bhushan Lohray, President, Zydus Research Centre)  
for CADILA HEALTHCARE LIMITED

To  
The Controller of Patents  
The Patent Office, at Mumbai

**FORM 2**

**The PATENT ACT, 1970  
(39 of 1970)**

**Provisional Specification**

**Improved process for the preparation of different forms of (S)-(+)-Clopidogrel  
bisulfate**

**CADILA HEALTH CARE LTD, Zydus Research Centre  
Zydus Tower, Satellite Cross Road, Sarkhej-Gandhinagar Highway, Ahmedabad-380015,  
Gujarat, India**

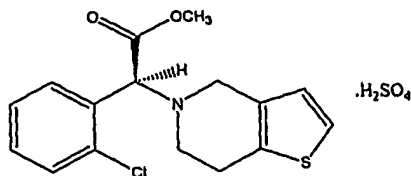
**The following specification describes the nature of the invention :**

## FIELD OF INVENTION

The present invention describes improved processes for the preparation of amorphous (S)-(+)-Clopidogrel bisulfate. More particularly, the present invention reveals improved processes for the preparation of amorphous polymorphs of (S)-(+)-Clopidogrel bisulfate hydrates, solvates, containing different form stabilizers and various pharmaceutical compositions containing the amorphous forms prepared according to the present invention. This invention further describes improved processes for the preparation of other crystalline polymorphs of S-(+)-Clopidogrel bisulfate, Form I, Form II and mixtures of amorphous forms prepared according to the present invention with Form I and Form II and pharmaceutical compositions containing them. (S)-(+)-Clopidogrel bisulfate an antiplatelet drug is currently being marketed for the treatment of atherosclerosis, myocardial infraction, strokes and vascular death. The present invention also describes a method of treatment of such cardiovascular disorders using the different forms of amorphous Clopidogrel bisulfate or mixtures thereof prepared according to the present invention, and pharmaceutical compositions containing them. The present invention relates to the use of the different forms of amorphous (S)-(+)-Clopidogrel bisulfate prepared according to the process disclosed herein and pharmaceutical compositions containing them for the treatment of cardiovascular disorders.

## BACKGROUND OF THE INVENTION

Clopidogrel bisulfate corresponds to the empirical formula  $C_{16}H_{16}ClNO_2S \cdot H_2SO_4$  and has a molecular weight 419.9. Chemically it is methyl (+)-(S)-alpha-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate sulfate (1:1), having the following structural formula.



Clopidogrel is an inhibitor of platelet aggregation and is marketed as an antianginal agent, antiplatelet agent and is found to decrease morbid events in people with established atherosclerotic cardiovascular disease and cerebrovascular diseases.

The therapeutic application of Clopidogrel as blood-platelet aggregation inhibiting agents and antithrombotic agent and its preparation is disclosed in U.S. Patent No. 4,529,596.

US Patent No 4,847,265 describes the process for the preparation of the hydrogen sulfate salt of Clopidogrel.

Various other strategies to prepare Clopidogrel are disclosed in WO 98/51681, WO 98/51682, WO 98/51689, WO 99/18110, US 5,036,156, US 5,132, 435, US 5,139,170, US 5,204,469 and US 6,080,875.

US Patent No. 4,847,265 discloses that the dextrorotatory enantiomer of formula (I) of Clopidogrel has an excellent antiagregant platelet activity, whereas the corresponding levorotatory enantiomer of (I) is less tolerated of the two enantiomers and is less active. US Patent No. 4,847,265 relates to the dextrorotatory enantiomer and its pharmaceutically acceptable salts with platelet aggregation inhibiting activity. However, the precision of determination of levoenantiomer in dextrorotatory enantiomer was not less than 4 %, implying thereby that the method used by the inventors cannot distinguish precisely a sample of S:R ratio 96:4 from a sample having the two enantiomers in the ratio 99.5:0.5 (*refer page 5, line 35-50, Patent No US 4,847,265*). Current regulatory requirements, however, require a high chiral purity (e.e. not less than 99%) for chiral drugs.

Subsequently filed Patent Application WO 99/65915 (US 6,429,210) titled "Polymorphic Clopidogrel hydrogensulfate form", which is herein incorporated by reference, discloses the existence of a specific polymorphic Form II of the hydrogen sulfate of (S)-(+)-Clopidogrel (m.p. =  $176 \pm 3$  °C). It is also disclosed in this patent application that the earlier processes described in the U.S. Patent 4,847,265 gives Form I (m.p.  $184 \pm 3$  °C). These two crystalline polymorphic forms I and II differed in their stability, physical properties, spectral characteristics and their method of preparation. However, both the polymorphs have similar bioavailability, as shown in their biocquivalence in healthy human volunteers.

Although U.S. patent No. 4,847,265 reports the formation of (S)-(+)-Clopidogrel bisulfate salt with m.p. 184 °C, it was disclosed as Form I only in patent application WO 99/65915. However, a reproducible and consistent method for the preparation of Form I with chirally pure material (ee >99%) was in doubt since chiral purity of the material (Clopidogrel bisulfate) with m.p.  $184 \pm 3$  °C, disclosed in U.S. Patent 4,847,265 was not precisely known (degree of imprecision 4 % as discussed above.).

In fact, we have observed that formation of Form I of (S)-(+)-Clopidogrel bisulfate with chiral purity >99% ee) is inconsistent and difficult to reproduce using the procedures reported in U.S. Patent 4,847,265 and WO 99/65915 whereas the formation of Form II is extremely facile and consistent with optically pure (S)-(+)-Clopidogrel free base.

We have disclosed improved processes for the manufacture of (S)-(+)- Clopidogrel bisulfate [Indian Patent Applications 84/MUM/2001 (WO 02059128, US application no. 2002177712); 335/MUM/2001 and 630/MUM/2001] which are cited herein in their entirety as reference.

We have also disclosed amorphous form of (S)-(+)- Clopidogrel bisulfate as hydrates, solvates (methanolates, ethanولات), containing different form stabilizers and process for their preparation [Indian Patent Applications 1190/MUM/2001 & PCT/IN03/00053]. We have also disclosed in this application mixtures of amorphous Clopidogrel bisulfate and Form I and amorphous Clopidogrel bisulfate and Form II which is also cited herein in its entirety as reference.

Amorphous Clopidogrel bisulfate and other solvated forms (1-butanol, 2-butanol, isopropanol, 1-propanol) as well mixtures of amorphous form and Form I & Form II and processes for preparing them have been disclosed in Teva's application no. WO 03/051362 A2, which is cited herein as reference. However, this application does not disclose amorphous Clopidogrel bisulfate hydrate, as well as amorphous Clopidogrel bisulfate containing form stabilizers like PEG or amorphous Clopidogrel bisulfate as methanolates or ethanولات

Teva's application also discloses process for preparing Form I & Form II of Clopidogrel bisulfate. The Form I is prepared by contacting the amorphous form disclosed therein in ethers preferably diethyl ether or MTBE as antisolvents. This process has the following disadvantages:

- i. Diethyl ether & MTBE are very volatile & inflammable hence are hazardous to work with;
- ii. The process cannot be scaled up to plant scale;
- iii. Problem of recovery of antisolvents further making the process economically unfeasible.

We herein disclose improved processes for preparing amorphous Clopidogrel bisulfate, amorphous Clopidogrel bisulfate hydrate, amorphous Clopidogrel bisulfate solvates, amorphous Clopidogrel bisulfate containing different form stabilizers, with high optical purity (ee >99%).

We also disclose improved processes for preparing Form I & Form II of Clopidogrel bisulfate. Also disclosed are amorphous Clopidogrel bisulfate, Form I & Form II of Clopidogrel bisulfate with characteristic impurity profile.

Crystalline solids normally require a significant amount of energy for dissolution due to their highly organized, lattice like structures. For example, the energy required for a drug molecule to escape from a crystal is more than from an amorphous or a non-crystalline form. It is known that the amorphous forms in a number of drugs exhibit different dissolution characteristics and in some cases different bioavailability patterns compared to the crystalline form (Konno T., *Chem. Pharm. Bull.*, 1990; 38: 2003-2007). For some therapeutic indications, one bioavailability pattern may be favoured over another. Therefore, it is desirable to have amorphous forms of drugs and a highly reproducible processes for their preparation.

### OBJECTIVES OF THE INVENTION

Accordingly, the present invention provides improved processes for preparation of amorphous form of (S)-(+)-Clopidogrel bisulfate (S).

Another objective is to develop improved processes for the preparation of amorphous Clopidogrel bisulfate hydrate.

Yet another objective is to develop improved processes for the preparation of amorphous Clopidogrel bisulfate solvates.

A still another objective is to develop improved processes for the preparation of amorphous Clopidogrel bisulfate containing different form stabilizers.

A still further objective is to develop a process for the preparation of Form I of Clopidogrel bisulfate.

A still further objective is to develop a process for the preparation of Form II of Clopidogrel bisulfate.

Yet another objective is to develop an improved process for the preparation of a mixture of the various amorphous forms described herein with Form I of Clopidogrel bisulfate.

Yet another objective is to develop a improved process for the preparation of a mixture of the various amorphous forms described herein with Form II of Clopidogrel bisulfate.



A still further objective is to disclose amorphous (S)-(+)-Clopidogrel bisulfate and its solvates (including hydrates), Form (I) & Form (II) of (S)-(+)-Clopidogrel bisulfate having characteristic impurity profile.

As an embodiment of the present invention pharmaceutical compositions containing the various amorphous forms of Clopidogrel bisulfate, Form I & Form II described herein and prepared according to the present invention are provided.

Also is provided a method of treatment and use of the various amorphous forms of Clopidogrel bisulfate, Form I & Form II described herein and prepared according to the present invention for the treatment of cardiovascular disorders, comprising administering, for example, orally a composition of the invention in a therapeutically effective amount.

## DESCRIPTION OF INVENTION

The present invention provides improved processes for the preparation of different amorphous forms of Clopidogrel bisulfate as described else where in the specification. The term "amorphous", as used herein, relates to solid material which lacks a regular crystalline structure. In a powder X-ray diffractogram such material gives no good intensity peaks. Without being bound by theory, it is believed and also observed that the amorphous solids offer the advantages of faster dissolution due to reduced dissolution energy requirement. Rapid dissolution is important for poorly soluble compounds administered orally, since there is a direct correlation between dissolution rate and bioavailability. Numerous instances have been recorded where only the amorphous form has adequate bioavailability. The term Clopidogrel base, Clopidogrel bisulfate used in the specification means (S)-(+)-Clopidogrel base & (S)-(+)-Clopidogrel bisulfate.

The various amorphous forms (hydrates, solvates, amorphous form containing form stabilizers) described in the specification can be prepared by any of the processes described below or used in combination.

- i) Clopidogrel base in suitable solvents is treated with dil.  $H_2SO_4$ , the solvent is evaporated & amorphous form precipitated by addition of a suitable antisolvent. Suitable solvents can be selected from methanol, ethanol, propanol, isopropanol, 1-butanol, 2-butanol; dichloromethane, dimethyl formamide, dimethyl acetamide, 1,4-dioxane, tetrahydrofuran

and the like or mixtures thereof. Suitable antisolvents may be selected from cyclohexane, heptane, *n*-hexane, pet ethers and the like or mixtures thereof.

- ii) Clopidogrel base in suitable solvents and water is treated with 98 %  $\text{H}_2\text{SO}_4$ , the solvent is evaporated & amorphous form precipitated by addition of suitable antisolvent. Suitable solvents can be selected from methanol, ethanol, propanol, isopropanol, 1-butanol, 2-butanol, dichloromethane, dimethyl formamide, dimethyl acetamide, 1,4-dioxane, tetrahydrofuran and the like or mixtures thereof. Suitable antisolvents may be selected from cyclohexane, heptane, *n*-hexane, pet ethers and the like or mixtures thereof.
- iii) Clopidogrel bisulfate in dichloromethane-water is treated with suitable bases, to obtain Clopidogrel base which is then treated with dil.  $\text{H}_2\text{SO}_4$  in suitable solvents, the solvent is evaporated & amorphous form precipitated by addition of suitable antisolvent. Suitable bases can be selected from NaOH, KOH, LiOH,  $\text{NaHCO}_3$ ,  $\text{Na}_2\text{CO}_3$ ,  $\text{K}_2\text{CO}_3$  and the like. Suitable solvents can be selected from methanol, ethanol, propanol, isopropanol, 1-butanol, 2-butanol, dichloromethane, dimethyl formamide, dimethyl acetamide, 1,4-dioxane, tetrahydrofuran and the like or mixtures thereof. Suitable antisolvents may be selected from cyclohexane, heptane, *n*-hexane, pet ethers and the like or mixtures thereof.
- iv) Clopidogrel bisulfate in dichloromethane -water is treated with suitable bases, to obtain Clopidogrel base which is then treated with 98 %  $\text{H}_2\text{SO}_4$  in mixture of suitable solvents and water, the solvent is evaporated & amorphous form precipitated by addition of suitable antisolvent. Suitable bases can be selected from NaOH, KOH, LiOH,  $\text{NaHCO}_3$ ,  $\text{Na}_2\text{CO}_3$ ,  $\text{K}_2\text{CO}_3$  and the like. Suitable solvents can be selected from methanol, ethanol, propanol, isopropanol, 1-butanol, 2-butanol, dichloromethane, dimethyl formamide, dimethyl acetamide, 1,4-dioxane, tetrahydrofuran and the like or mixtures thereof. Suitable antisolvents may be selected from cyclohexane, heptane, *n*-hexane, pet ethers and the like or mixtures thereof.
- v) Clopidogrel camphor-sulfonate in suitable solvents like dichloromethane, dichloroethane, chloroform and the like and water is treated with suitable bases, to obtain Clopidogrel base which is then treated with dil.  $\text{H}_2\text{SO}_4$  in suitable solvents, the solvent is evaporated & amorphous form precipitated by addition of suitable antisolvent. Suitable bases can be selected from NaOH, KOH, LiOH,  $\text{NaHCO}_3$ ,  $\text{Na}_2\text{CO}_3$ ,  $\text{K}_2\text{CO}_3$  and the like. Suitable solvents can be selected from methanol, ethanol, propanol, isopropanol, 1-butanol, 2-butanol, dichloromethane, dimethyl formamide, dimethyl acetamide, 1,4-dioxane,

tetrahydrofuran and the like or mixtures thereof. Suitable antisolvents may be selected from cyclohexane, heptane, *n*-hexane, pet ethers and the like or mixtures thereof.

- vi) Clopidogrel camphor-sulfonate in in suitable solvents like dichloromethane, dichloroethane, chloroform and the like and water is treated with suitable bases, to obtain Clopidogrel base which is then treated with 98 % H<sub>2</sub>SO<sub>4</sub> in mixture of suitable solvents and water, the solvent is evaporated & amorphous form precipitated by addition of suitable antisolvent Suitable bases can be selected from NaOH, KOH, LiOH, NaHCO<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub> and the like. Suitable solvents can be selected from methanol, ethanol, propanol, isopropanol, 1-butanol, 2-butanol, dichloromethane, dimethyl formamide, dimethyl acetamide, 1,4-dioxane, tetrahydrofuran and mixtures thereof. Suitable antisolvents may be selected from cyclohexane, heptane, *n*-hexane, pet ethers and the like or mixtures thereof.

Various polyethylene glycols (PEG) 200,400,800,900,1000,1200,2000 and 4000 can also be used as amorphous form stabilizers in any of the processes described above.

Alternatively, the processes [(i)-(vi)] described above can be repeated by using the Clopidogrel base, Clopidogrel bisulfate and Clopidogrel camphor-sulfonate prepared according to the improved process described by the applicant in WO 02059128/ US 2002177712.

The present invention also describes improved process for the preparation of Form I of Clopidogrel bisulfate from the different amorphous forms prepared according to any of the processes of the present invention. The Form I is obtained by treating the above amorphous forms in mixture of diethyl ether-heptane, diethyl ether-hexane, diethyl ether-pet ethers in various combination and proportion, with a view to enhance operational safety, scaleability and simplicity.

It also describes improved process for the preparation of Form II of Clopidogrel bisulfate from the different amorphous forms prepared according to any of the processes of the present invention. Form II is obtained by stirring the different amorphous forms in solvents like acetone, MTBE and the like or their mixtures.

The processes for preparing various amorphous forms of (*S*)-(+)-Clopidogrel bisulfate, Form I & Form II according to the present invention are

- not hazardous as it does not use volatile chemicals.
- scalable at plant level and so industrially useful

- easy to operate

The present invention also discloses amorphous forms of Clopidogrel bisulfate having a characteristic impurity profile. The amorphous forms of Clopidogrel bisulfate of the present invention has (S)-(+)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide as impurity, not exceeding 0.5% by weight.

The amorphous forms of (S)-(+)-Clopidogrel bisulfate including hydrates/solvates (methanolates, ethanolates and the like), Form I & Form II of (S)-(+)-Clopidogrel bisulfate prepared according to the processes of the present invention can be characterized by their melting point, physical characteristics, X-ray powder diffraction pattern, DSC, thermogravimetric analysis, differential scanning calorimetry, diffused reflection IR absorption and/or by its solid state nuclear magnetic resonance spectrum and % content of water, methanol, ethanol and other solvates mentioned in processes (i) to (vi), including form stabilizers like various PEGs described above.

The different forms of amorphous (S)-(+)-Clopidogrel bisulfate hydrates/solvates (methanolates, ethanolates and the like), Form I & Form II of (S)-(+)-Clopidogrel bisulfate prepared according to the processes of the present invention may be administered orally, parenterally or rectally without further formulation, or as a simple solution in water or any pharmaceutically acceptable liquid carrier. The drug substance of the present invention may also be filled in a capsule directly for oral administration. However, it is preferred that the drug substance is formulated with one or more excipients to prepare a pharmaceutical composition, for example, an oral dosage form.

Another aspect of the present invention aims at providing the various pharmaceutical compositions of the different amorphous forms of (S)-(+)-Clopidogrel bisulfate, Form I & Form II of (S)-(+)-Clopidogrel bisulfate containing active ingredients.

According to the present invention, the various amorphous forms of (S)-(+)-Clopidogrel bisulfate, Form I & Form II prepared according to the processes of the present invention is formulated in pharmaceutical compositions for oral use containing required amount of the active ingredient per unit of dosage, in combination with at least one pharmaceutical excipient in the form of tablets, sugar coated tablets, capsules, injectable solutions, granules or a syrup. They can also be administered rectally in the form of suppositories or can be parentally administered in the form of an injectable solution.

In another embodiment of the present invention a method of treatment and use of the different amorphous forms of (S)-(+)-Clopidogrel bisulfate, Form I & Form II prepared according to the

processes of the present invention, for the treatment of cardiovascular disorders is provided, comprising administering, for example, orally or in any other suitable dosage forms, a composition of the invention in a therapeutically effective amount.

Dated this 1st day of NOVEMBER 2003

Signature B. B. Lohray

Dr. B. B. Lohray  
(President, Zydus Research Centre)  
*For Cadila Healthcare Limited*

To  
The Controller of Patents  
The Patent Office, at Mumbai

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